IS ASTHMA *ALWAYS* AN ALLERGIC DISEASE?*

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Francis Rackemann was a remarkable Boston physician who made major contributions to our understanding of asthma and respiratory allergies during the first half of this century. In 1918, he published his analysis of 150 cases of bronchial asthma and introduced the term extrinsic asthma to denote asthmatic reactions which can be attributed to hypersensitivity to foreign substances (1). In contrast, the disease is "intrinsic" according to Rackemann when patients don't promptly get better spontaneously after admission to the hospital.

Indeed, to the present time, textbooks have found it useful to contrast these two forms of asthma as follows: extrinsic or allergic asthma has its usual onset in childhood, affects boys 2–3 times more frequently than girls, is associated with allergic rhinitis and atopic dermatitis in a triad of disorders with a strong familial tendency, and is usually accompanied by high total serum IgE and numerous positive IgE antibody tests. The non-allergic or "intrinsic" form of asthma often begins after age 30, affects females preferentially, is associated with chronic sinusitis and nasal polyps, and evidence for genetic transmission is weak. In these asthmatic patients, total serum IgE is ordinarily quite low and only rarely are IgE antibodies to environmental allergens detectable.

On the other hand, at the levels of histopathology and respiratory physiology, all efforts to distinguish two forms of asthma have been in vain. Both intrinsic and extrinsic asthma qualify pathologically as "chronic desquamating eosinophilic bronchitis," a descriptive definition of asthma first applied by Prof. Charles Reed (2). Pulmonary function testing also does not distinguish intrinsic and extrinsic forms except that the obstructive defects are usually more severe in the intrinsic form of asthma which quite commonly becomes steroid dependent (3, 4).

The epidemiology of asthma also supports the notion of two diseases with differing natural histories (5). The relationship of age of onset to atopic history in 1,125 consecutive clinic patients in rural Iowa is shown in Figure 1. Some 87% of those who developed asthma under ten years

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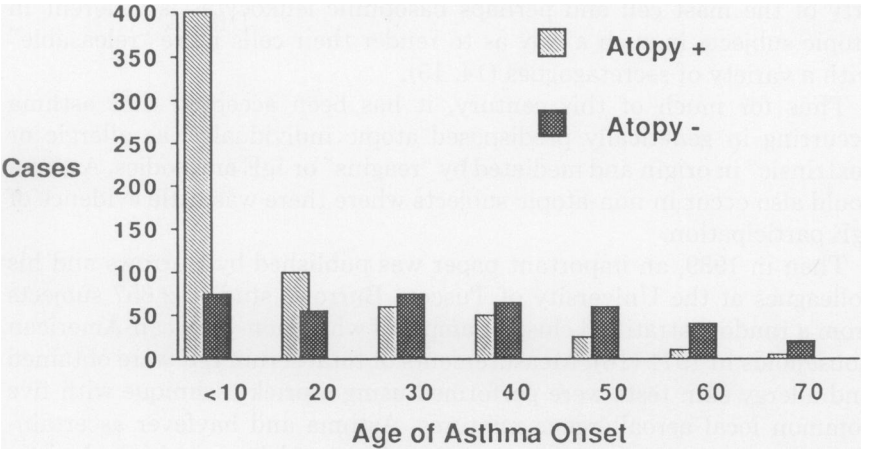

FIG. 1. Relationship of age of asthma onset to atopic history in 1125 clinic patients in rural Iowa. Adapted from Reference 6.

of age had a positive atopic history. In contrast after age 30, most new cases of asthma involved patients without an atopic background (6). In this allergen rich midwest community, 75% of the cases of asthma could be attributed to allergic or extrinsic causes. In other areas of the world with much lower prevalences of asthma and allergic rhinitis, the age of onset for asthma is often considerably later even when extrinsic in type (5).

Allergic or extrinsic asthma is often associated in families with two other disorders which constitute the atopic triad: allergic rhinitis and atopic dermatitis. Numerous studies over many decades have shown that the atopic diathesis has two distinguishable features. First, atopy enhances synthesis of IgE antibody to a wide variety of environmental allergens. As a consequence, total serum IgE is elevated to differing degrees in all three disorders (7, 8). Second, and often overlooked, is the fact that atopic patients facilitate in some manner the clinical expression of mast cell-dependent disorders. This is especially true for IgE-dependent mast cell activation as illustrated by the fact that atopic patients have higher mortality rates from anaphylactic reactions to drug and bee sting allergens (9, 10), despite the fact that as a group they do not mount more frequent or more intense IgE antibody responses to either drugs or bee sting proteins (11, 12).

But it is equally true that atopic patients are at greater risk for anaphylactoid reactions to radiographic contrast media where neither IgE antibody nor any immune mechanism is likely involved in the pathogenesis (13). These observations suggest that a biochemical prop-

erty of the mast cell and perhaps basophilic leukocytes is different in atopic subjects in such a way as to render their cells more "releasable" with a variety of secretagogues (14, 15).

Thus for much of this century, it has been accepted that asthma occurring in genetically predisposed atopic individuals was allergic or "extrinsic" in origin and mediated by "reagins" or IgE antibodies. Asthma could also occur in non-atopic subjects where there was little evidence of IgE participation.

Then in 1989, an important paper was published by Burrows and his colleagues at the University of Tuscon. Burrows studied 2,657 subjects from a random stratified cluster sample of white non-Mexican-American households in 1971 (16). Measurements of total serum IgE were obtained and allergy skin tests were performed using a prick technique with five common local aeroallergens mixtures. Asthma and hayfever ascertainment was by questionnaire. A categorical model of multiple logistic regression analysis was used to evaluate the independent effects of IgE level, skin test reactivity and smoking habits on the prevalence of asthma and rhinitis.

As seen in Figure 2, the prevalence of asthma in all three age groups was shown to be strongly related to serum IgE expressed as a Z score which was age and sex adjusted. There were no cases of asthma among

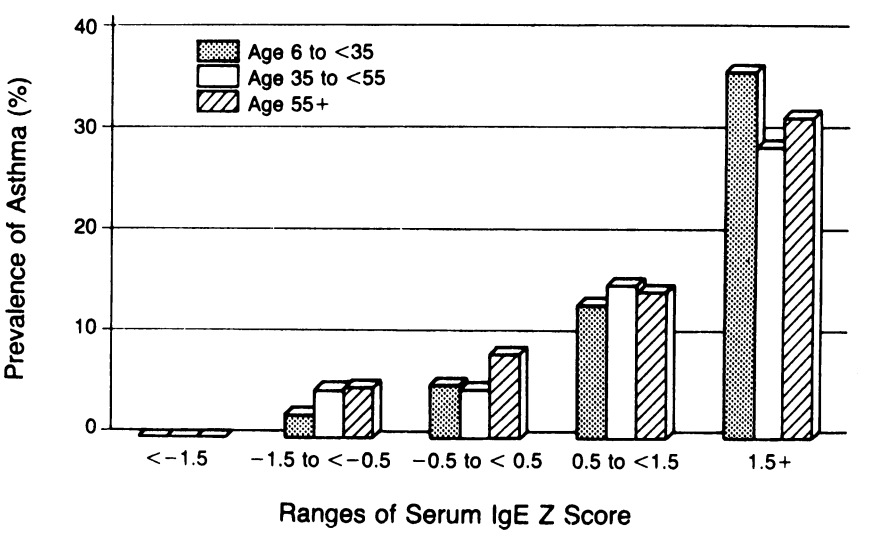

FIG. 2. Prevalence of asthma related to serum IgE levels expressed as standard deviations from age- and sex-adjusted mean (z- scores) in 1662 white non-Mexican-American subjects with completely negative allergy skin tests. Reproduced with permission from Reference 16.

subjects with serum IgEs < 1.5 standard deviations below the mean. In contrast, the prevalence of asthma averaged 30% among those with IgE levels higher than 1.5 standard deviations above the mean. As might be expected, a similar relationship existed between skin test scores and the prevalence of asthma though the association was weaker (16).

In order to examine the effect of IgE levels independent of confounding variables, a logistic regression analysis was performed (Fig. 3). The odds ratio of having asthma (open circles) or hayfever (closed circles) is shown as a function of serum IgE after correction for age, sex, smoking status and skin test index. A remarkable linear relation between the log odds ratio for having asthma and increasing levels of IgE was observed (solid line). In contrast the relationship of IgE to rhinitis was weaker and seen only at higher IgE levels. It is also noteworthy that the odds ratio was statistically significant even at the very low serum IgE level of 5 IU/ml.

This striking finding prompted examination of the relationship of IgE levels and asthma among subjects in the population who ordinarily would be considered to have the "intrinsic" form of the disease as evidenced by negative skin tests. Burrow's analysis revealed almost exactly the same prevalence rates for asthma for various IgE Z scores in these 1,662 subjects with completely negative allergy skin tests, as previously ob-

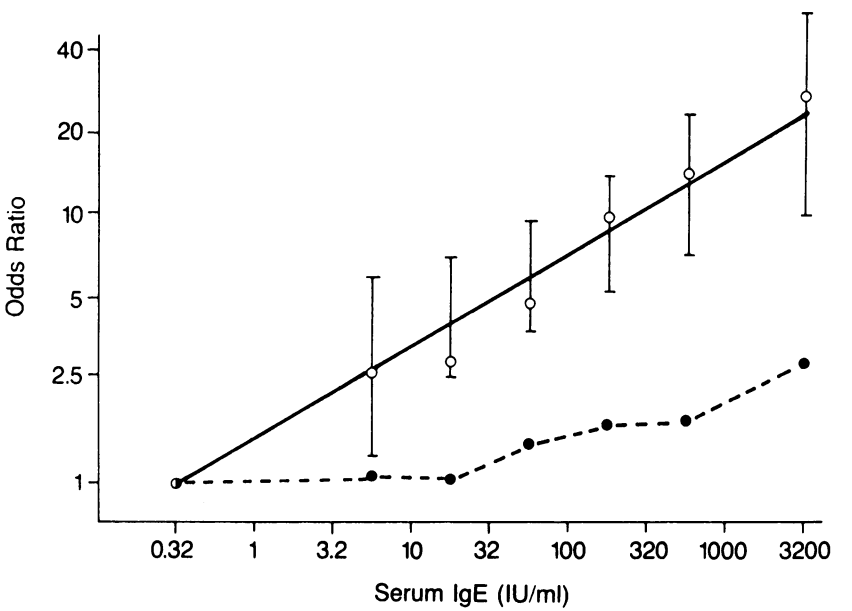

FIG. 3. Relative risk (odds ratio) of asthma (open circles) and allergic rhinitis (closed circles) as a function of log serum IgE. Solid line shows logistic regression analysis for asthma function. Reproduced with permission from Reference 16.

served for the entire population (Fig. 4). He concluded that even among intrinsic asthmatics, IgE levels are strongly related to the prevalence of asthma.

This paper and its principal conclusion have been criticized for a number of perceived methodological faults, largely without justification in my view. On the other hand, this paper was championed by a number of enthusiastic allergists who were happy to abandon the notion of intrinsic asthma in favor of a unitary allergy hypothesis which entailed the notion that there must be important allergens for asthma that we haven't yet discovered.

To my knowledge, these epidemiologic findings have not been reproduced by another study to date. Recently, however, Malcolm Sears, collaborating with the Burrows' group for analysis, reported in the *New England Journal* an important finding from a New Zealand study which some will say adds credence to the Burrows' hypothesis (17). In the New Zealand study, total serum IgE and airway responsiveness to inhaled methacholine were related to the presence or absence of asthma and other atopic diseases in 562 eleven-year-old New Zealand children. As expected, the prevalence of current diagnosed asthma was twice as high among the group of boys as among the girls (13% vs. 6%), though the mean serum IgE levels in boys and girls did not differ. And not unexpectedly, the prevalence of diagnosed asthma was strongly related to the serum IgE level even when concomitant diagnoses of allergic rhinitis or

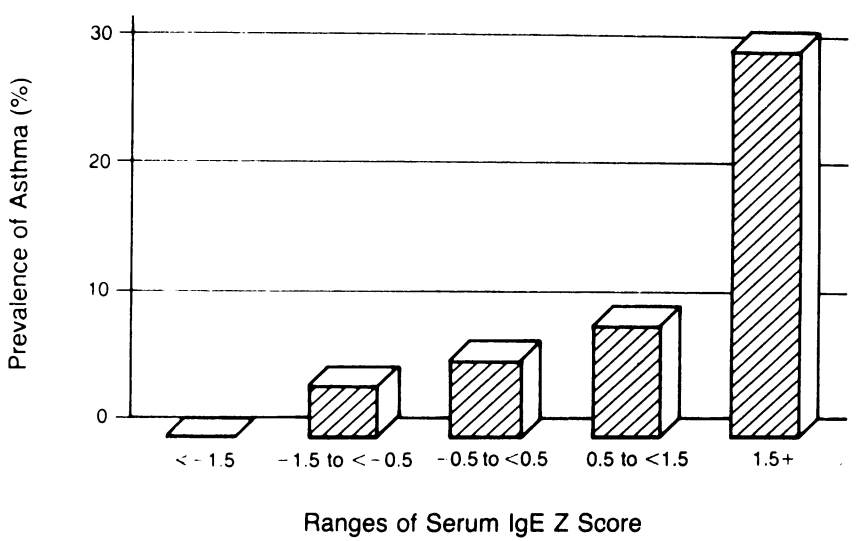

FIG. 4. Prevalence of asthma related to serum IgE levels in 1662 subjects with negative allergy skin tests. Reproduced with permission from Reference 16.

eczema were controlled. Airway hyperresponsiveness to methacholine, a strong marker for active asthma, also correlated very highly with serum IgE levels.

The striking finding of the Sears' study was that the relationship between methacholine sensitivity and serum IgE level remains highly significant even after the exclusion of all children with a history of asthma, wheezing, hayfever or eczema (Fig. 5). The relationship holds if either of two suggested thresholds for methacholine sensitivity is employed.

So even in asymptomatic children with no evidence of atopic disease, it was possible to show a strong relationship between serum IgE level and the prevalence of bronchial hyperreactivity. Since bronchial hyperreactivity is considered by most in the field as a hallmark of chronic allergic airway inflammation (18), this finding is compatible with the suggestion that ongoing IgE-dependent allergic inflammation may in

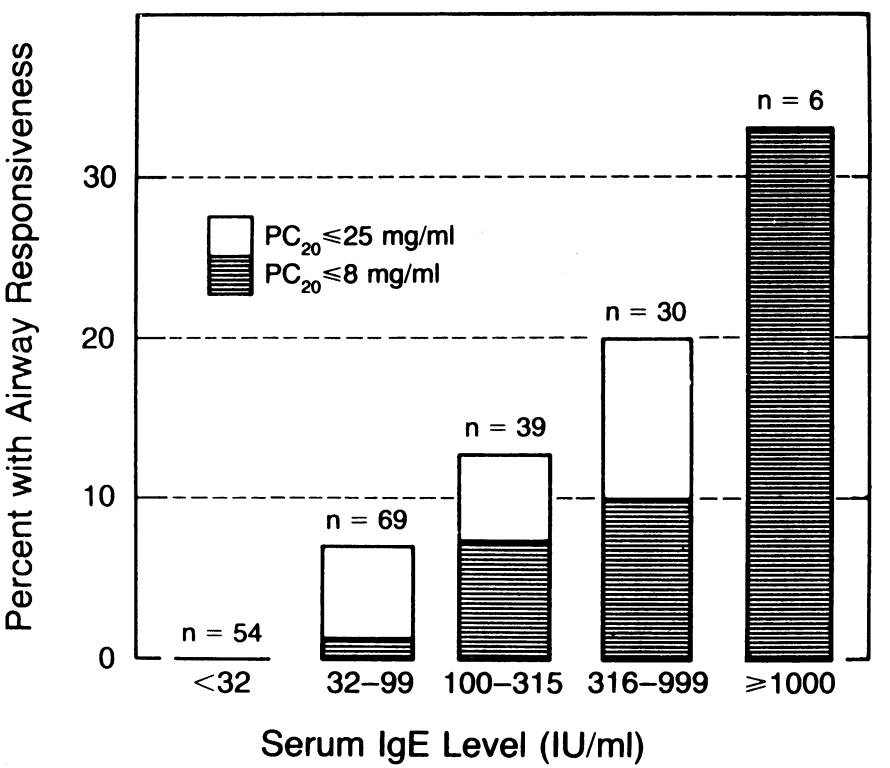

FIG. 5. Airway responsiveness as a function of serum IgE level among 562 eleven-year-old New Zealand children without history of asthma, wheezing hay fever or eczema. Reproduced with permission from Reference 17.

some children lead to asymptomatic bronchial hyperreactivity. If correct, this has important implications since other investigators have shown that bronchial hyperreactivity in asymptomatic subjects is a strong risk factor for the later development of asthma (19, 20).

I suspect that this new finding will rejuvenate the unitary allergy hypothesis and prompt new calls for expeditions to find occult allergens that are responsible for what we have previously considered "intrinsic" disease. And such research is of course appropriate. I personally remain skeptical and continue to believe with Rackemann that most non-atopic patients with asthma clearly have a disease of different origin. The severity and poor prognosis of asthma in non-atopic subjects together with its female predominance and associated rhinosinusitis is not easily ignored.

Multiple lines of experimental and clinical evidence suggest that chronic allergic inflammation leads to airway hyperreactivity which can lead to symptomatic asthma. Perhaps the best-studied example is occupational asthma where asymptomatic workers with repeated exposure to a potent chemical or other sensitizing allergens can develop IgE-dependent asthma with attendant bronchial hyperreactivity which persists in some cases for many years after exposure to the offending allergen has ceased (21, 22). But does this allergic inflammation *always* have to be IgE-dependent? What *is* reasonable to expect is that allergic inflammation will be *mast cell dependent* and *may be* IgE-dependent. As Figure 6 indicates, mast cell mediators produce immediate bronchoconstriction and recruit other inflammatory cells, particularly eosinophils, into the

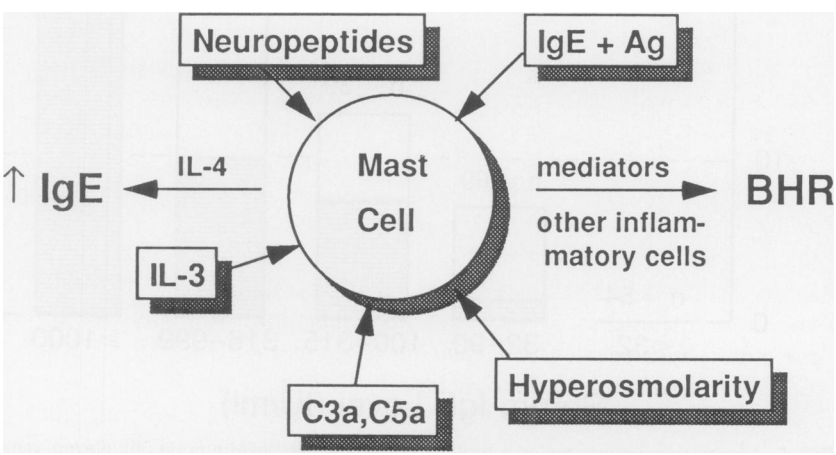

FIG. 6. Stimuli for mast cell activation/growth and resultant cytokine and mediator production (see text).

allergic focus. This panoply of mediators and cells is believed by most investigators to be quite sufficient to explain the origin of bronchial hyperreactivity in chronically inflamed respiratory tissue (23).

But we also know that mast cells can be activated and modulated by stimuli other than IgE antibody. Interleukin 3 which controls the differentiation of mast cells may also control its threshold for activation (24). The hyperosmolar milieu can also potentiate mediator release (25). The complement derived C3a and C5a anaphylatoxin peptides can activate mast cells thereby providing another potential immune mechanism (26). Finally, there is much current interest in the role of the autonomic nervous system in modulating mast cell function, particularly non-adrenergic, non-cholinergic pathways (27). Our current understanding allows that a variety of stimuli, not just IgE-mediated events, could promulgate repeated mast cell triggering leading to chronic allergic-type inflammation and possibly bronchial hyperreactivity.

Now one can immediately see this explanation as a restatement of the possibility of so-called "intrinsic disease." But how can we reconcile this possibility with the two compelling epidemiologic studies which relate serum IgE levels to asthma and bronchial hyperreactivity, even in non-atopic and asymptomatic populations? An intriguing recent observation suggests one possibility.

Interleukin 4 is an essential signal for the synthesis of IgE and is now believed to regulate the transcription of the epsilon gene (28). It is generally believed that IL-4 is provided by a TH2-type helper T cell to initiate the switch to IgE synthesis (29). Recent work from William Paul's lab at the NIH has indicated that in mouse bone marrow, the predominant source of IL-4 synthesis is a non-T, non-B cell which very much resembles a basophil/mast cell (30). Furthermore, my colleague Marshall Plaut, working in Dr. Paul's laboratory has shown that activation of mast cells leads to the synthesis of a number of interleukins including IL-4 (31). If this observation is born out in human studies which are now underway, it would provide one possible explanation of the association of IgE with bronchial reactivity and asthma. In patients with "intrinsic" disease, chronic mast cell activation in the lung could produce sufficient quantities of IL-4 and perhaps other regulatory cytokines to enhance IgE synthesis to some degree. This is clearly speculation for the moment, and there are certainly other potential ways for IgE to be *associated* with mast cell activation without requiring that the associated IgE is *mediating* the activation.

So we return to the original question, is asthma *always* an allergic disease? If we define "allergic" in the narrow sense as IgE-dependent then I believe the answer is probably not, the recent epidemiologic studies reviewed here notwithstanding. A unitary hypothesis for the pathogenesis

of a disease is always appealing, but rarely realized when the disease is as complex as asthma. If we adopt a broader definition of "allergic" to mean "mast cell-dependent" then most will hardily endorse the notion that allergic inflammation is *the* cause of asthma. The intricacies of this final mast-cell dependent pathway of the asthmatic diathesis are now being carefully worked out in detail. In the future we can expect much greater insight into the multiple biological pathways which impinge upon this fascinating disease.

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